Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group

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Abstract

Objective To determine whether poor reporting of methods in randomised controlled trials reflects on poor methods.

Design Observational study.

Setting Reports of randomised controlled trials conducted by the Radiation Therapy Oncology Group since its establishment in 1968.

Participants The Radiation Therapy Oncology Group.

Outcome measures Content of reports compared with the design features described in the protocols for all randomised controlled trials.

Results The methodological quality of 56 randomised controlled trials was better than reported. Adequate allocation concealment was achieved in all trials but reported in only 42% of papers. An intention to treat analysis was done in 83% of trials but reported in only 69% of papers. The sample size calculation was performed in 76% of the studies, but reported in only 16% of papers. End points were clearly defined and α and β errors were prespecified in 76% and 74% of the trials, respectively, but only reported in 10% of the papers. The one exception was the description of drop outs, where the frequency of reporting was similar to that contained in the original statistical files of the Radiation Therapy Oncology Group.

Conclusions The reporting of methodological aspects of randomised controlled trials does not necessarily reflect the conduct of the trial. Reviewing research protocols and contacting trialists for more information may improve quality assessment.

Introduction

Evaluation of the quality of published clinical research is central to informed decision making. Information on trial quality is particularly important during peer review or when results from individual studies are evaluated in systematic reviews or meta-analyses.[1 2] The quality of research should always be considered when a report is used in decision making in health care. Poorly conducted and reported research seriously compromises the integrity of the research process, especially if biased results receive false credibility.[3]

Many efforts have been made to improve the quality of studies and their related publications. The best example was the publication of the Consolidated Standards of Reporting of Trials (CONSORT) statement to improve the quality of trial reports.[3] Such efforts to improve the quality of clinical research, however, imply that if certain design or methodological features are not reported then they were not done. Ideally, assessment of the quality of clinical research should not only address reporting but also the original design and intended plan for its conduct and analysis as specified in the trial's research protocol. The importance of linking the final report of clinical trials with their original research protocols led some authors to argue that no randomised controlled trial should be conducted without publication of its research protocol.[4] The reasons behind this are that critical comments may be encouraged leading to improvements in trial design, publication can be coupled with trial registration, the original protocol can be compared with what was subsequently done, and investigators can more easily appreciate what research is being conducted in their areas of interest.[4] More importantly, publication of research protocols is one of the best ways to minimise bias by explicitly stating a priori hypotheses and methods without the prior knowledge of results.[5] Many randomised controlled trials are preceded by the preparation of a written protocol, which describes the conduct of the trial more comprehensively than is possible in many journal articles, and making these protocols available would provide much useful additional information. We aimed to test the assumption that poor reporting reflects poor methods by comparing research protocols with the information published in the final reports of a set of randomised controlled trials.

Methods

We studied randomised controlled trials conducted by the Radiation Therapy Oncology Group. This is a national clinical cooperative group with a focus on the development of studies to improve survival and the quality of life of patients with cancer. It was established in 1968 and is publicly funded by the National Cancer Institute in the United States. The group consists of both clinical and laboratory investigators from over 260 institutions across the United States and Canada, and its membership includes nearly 90% of all comprehensive and clinical cancer centres designated by the National Cancer Institute.[6] Before activation, the group's research protocols must pass through a rigorous peer review process and be reviewed and approved through its own committee system and the National Cancer Institute. Development of a protocol consists of six phases (box).[6]

Our analysis included data related to primary outcomes from all terminated phase III trials conducted by the Radiation Therapy Oncology Group since its establishment in 1968. We extracted data on methodological domains that have been acknowledged as vital

for minimising bias in the conduct and analysis of randomised controlled trials.[7] The effect of chance is usually minimised by appropriate planning of the trial's size, through a statistical power analysis using estimates for the expected differences between the interventions and prespecified type I (α) and type II (β) error levels.[7] To investigate systematic bias we extracted data on the quality of the randomisation process (selection bias) and drop outs (attrition bias).[8] Since the primary outcome was survival in most of the studies, we did not consider quality related to observer bias, such as the use of placebo or independent reading of outcomes (there were only three placebo controlled trials). We extracted data from all papers and protocols. The accuracy of this data was verified by the group's statistical centre.

Results

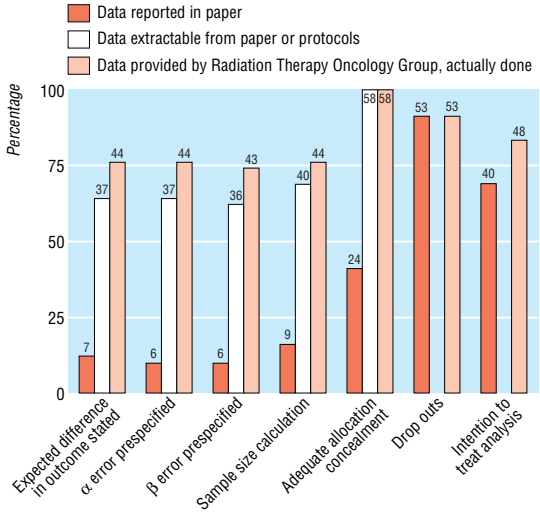
Overall, there were 59 terminated phase III randomised controlled trials, three of which had not been published. We found 58 published papers for the remaining 56 protocols for use in our study. The figure summarises the results according to information from the papers, protocols, and the Radiation Therapy Oncology Group's statistical office. This shows that the reporting of methods in the publications does not necessarily reflect the methodological quality of the associated protocols. For example, a priori sample size calculations were performed in 44 (76%) trials, but this information was given in only nine of the 58 published papers (16%). Although all trials had adequate allocation concealment (through central randomisation), this was reported in only 24 (41%) of the papers. From our initial data extraction, we found that 40 (69%) of these trials used an intention to treat analysis. This number was increased to 48 (83%) after verification by the Radiation Therapy Oncology Group. End points were clearly defined, and α and β errors were prespecified in 44 (76%) and 43 (74%) trials, respectively, but only reported in six (10%) of the papers. Interestingly, reporting of drop outs was meticulous; we found no difference in frequency (91%) between data presented in the papers and those in the original files.

Discussion

Poor reporting of randomised controlled trials may not indicate poor quality of the trials themselves. We are aware of two other studies that reported empirical assessments of this relation. One study evaluated the quality of 63 randomised controlled trials of breast cancer treatment. Data were extracted from publications related to these trials and the results compared with the information provided by the principal investigators. The study concluded that faulty reporting reflected faulty methods.[9] Another study, however, concluded that even well designed and conducted trials may be badly reported.[2] This conclusion was drawn indirectly from an assessment of three key indicators of quality: adequate allocation concealment, appropriate blinding, and use of intention to treat analysis.[2] Unlike our study, neither of these studies reported a comparison of the quality of reporting with the methods specified in the original research protocols.

In general, the Radiation Therapy Oncology Group and, we predict, other cooperative oncology groups sponsored by the National Cancer Institute, have conducted research of good quality. Our study is the first formal investigation of this and, we believe, the first examination of the methodological quality of randomised controlled trials performed by a cooperative oncology group.

The relation between poor reporting and poor methods was raised in 1980 in a report on patient registration, randomisation, and the importance of avoiding bias in cooperative oncology trials.[10] This may have helped the cooperative oncology groups to be especially aware of methodological issues relating to trials and before the start of modern research on methodological quality.[11] Consequently, for cooperative oncology groups such as the Radiation Therapy Oncology Group, even if the published description of the methods of a randomised controlled trial is poor, the quality of the trial should not be assumed to be poor. It is important to note, however, that our findings are based on a select sample of trials, which may not be representative of randomised controlled trials. Further studies to confirm the generalisability of our findings are needed and would be useful.



Quality of reporting compared with actual methodological quality of 56 randomised controlled trials (58 reports) conducted by the Radiation Therapy Oncology Group, based on information from published reports, protocols, and verification by the group. Absolute numbers of reports are shown

Phases in development of a trial protocol by Radiation Therapy Oncology Group

- Approval of concept
- Review and approval of protocol among group members
- Review by headquarters, including statistics, data management, quality assurance, protocol administrator, and review by the institutional review board
- Review by National Cancer Institute
- Activation of protocol
- Revision of protocol

Another important point relates to any assumptions that trials published before the 1996 CONSORT statement are more likely to be of poorer quality than those published after it.[3] The CONSORT statement contains several methodological elements that should be followed to eliminate biased results. The intention of this statement was to improve the conduct, integrity, and reporting of randomised controlled trials.[3] Our results show that studies conducted by the Radiation Therapy Oncology Group were of high quality even before publication of the CONSORT statement. It was the reports of the randomised controlled trials that showed deficiencies in their description of the methods used in the trials, not the trials themselves. Our findings indicate that although researchers in the Radiation Therapy Oncology Group were cognisant of key features in the design and conduct of good quality trials, they were less aware of the need to report these to a standard that would meet contemporary (CONSORT) requirements.

It is still appropriate to expect that the CONSORT statement will contribute to the conduct of higher quality randomised controlled trials in the future, since it incorporates and highlights many of the elements needed to perform a trial adequately. We agree with the call for all journals to adopt the policy of only publishing the report of a randomised controlled trial if it follows the CONSORT requirements. This is supported by empirical data that are now emerging about the usefulness of the CONSORT statement. For example, one study compared the quality of reports of trials before and after the CONSORT statement and found that the statement was associated with an improvement in the quality of reports.[12] Further improvements in the quality of the conduct and reporting of clinical research would arise with the publication of research protocols.[4]

Contributors: HPS and BD conceptualised the study, were involved in all aspects of the study, and wrote the first draft of the paper. SD and AK contributed to the study design, collection of data, analysis and interpretation of the data, and writing the report. MC contributed to the study design, interpretation of the data, and writing the report. CS and SS contributed to the collection of data and writing the report. BD will act as guarantor for the paper.

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What is already known on this topic

Assessment of the quality of research evidence is central to informed decision making

The quality of randomised controlled trials is often based on the quality of reporting

What this study adds

Poor reporting of methods in randomised controlled trials may not reflect on poor methods themselves

Evaluation of research protocols and contacting trialists should be integral to assessing the quality of such trials

Competing interests: MC is director of the UK Cochrane Centre, which is funded by the NHS research and development programme and part of the international Cochrane Collaboration. The collaboration produces systematic reviews of health care, including randomised trials, but the views expressed here are not necessarily those of the official policy of the Cochrane Collaboration.

Ethical approval: This study was approved by the University of South Florida Institutional Review Board (No 100449).

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Commentary: The quality of randomised controlled trials may be better than assumed

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continued over

As readers of published articles, it is reassuring to know that the quality of published data is probably better than expected from the reporting of the methods. Soares and colleagues have addressed the discrepancies between the proposed methods in original research protocols and those reported in the final article for all 56 randomised controlled trials conducted by the Radiation Therapy Oncology Group since its creation in 1968. Good quality experimental designs were more often adhered to during the conduct of the studies than suggested by the final reports.

As readers of systematic reviews, however, we may have underestimated the quality of experimental methods, especially if reviewers had not checked the original protocols. This may have led to the exclusion of some potentially good quality papers from systematic

reviews.[1] This would also affect the scoring of quality of papers as a part of a meta-analysis.[2 3] Soares and colleagues suggest that this problem can be avoided by accessing the original protocols and contacting trialists to check the accuracy of reported methods. Authors should also adhere to the Consolidated Standards of Reporting of Trials (CONSORT) statement.[4]

In the near future, papers may be accompanied by internet links to their original protocol and data, allowing researchers to download crude data for meta-analysis. Until that time, it should be borne in mind that although papers fail to report important design and methodological features, they were probably done, especially if the papers are authored by a body such as the Radiation Therapy Oncology Group, the protocols of which undergo rigorous review.

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Drug points

Rash and acute nephritic syndrome due to candesartan

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A 73 year old man presented with a two day history of a pruritic rash and oedema affecting both lower legs. He had had hypertension for three years, for which he had been taking candesartan, an angiotensin II receptor antagonist, for the past two years. He was not taking any other medications or preparations. He had no infective, gastrointestinal, or respiratory symptoms and no arthralgias.

Examination showed non-palpable, non-tender purpura affecting both legs, with pitting oedema, and urticarial lesions on the left knee and anterior chest. Testing of urine was positive for protein and blood. Urine microscopy showed >100 erythrocytes per 10^6/l; the urine protein:creatinine ratio was 0.15 (normal range <0.04), serum creatinine was 90 µmol/l (70-120 µmol/l), C reactive protein was 117 mg/l (0-6 mg/l), and the erythrocyte sedimentation rate was 32 mm/hour (1-20 mm/hour). A provisional diagnosis of Schönlein-Henoch purpura due to candesartan was made, and the medication was stopped. Serum immunoglobulin A concentration, however, was normal. The results of an autoantibody screen and testing for antineutrophil cytoplasmic antibodies were negative, complements were normal, and cryoglobulins were not detected. A skin biopsy showed lymphocytic vasculitis involving vessels in the papillary and mid-dermis, as well as spongiosis and moderate orthokeratosis. We believed the features to be consistent with a drug reaction. The rash and microscopic haematuria resolved completely within a week of stopping candesartan and C reactive protein concentration became normal three weeks after presentation, though proteinuria took 10 weeks to resolve.

Irbesartan, another angiotensin II receptor antagonist, was the highest volume drug prescribed for hypertension in Australia on the pharmaceutical benefits scheme for the year ending December 2002. A major reason for the popularity of this class of drugs is their side effect profile, shown to be similar to that of placebo in double blind studies.[1] Major side effects published in the literature, however, include hepatotoxicity, pancreatitis, angio-oedema, acute deterioration in renal function, and dysgeusia. Two cases of Schönlein-Henoch purpura have been described as being associated with therapy with losartan.[2 3] Both had a similar presentation to the case described above, with purpuric rash, pedal oedema, microscopic haematuria, proteinuria, raised C reactive protein concentration, and rapid resolution when the drug was stopped. Both cases, however, were associated with raised serum IgA concentration and deposits in the dermal vessel walls on histology.

From 1999 until November 2002, seven cases of rash were reported to the Adverse Drug Reaction Advisory Committee in Australia, in which candesartan was the sole possible agent responsible. No cases of nephritis have been reported to the committee to date. Similarly, the manufacturer of candesartan (AstraZeneca) has not received any reported cases of nephritis with candesartan. In conclusion, the angiotensin II receptor antagonists are a very well tolerated group of antihypertensive drugs, but they should be considered to be a potential cause of rash or acute nephritic syndrome in any patients presenting with those symptoms, regardless of how long they have been taking the drug.

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Competing interests: None declared.

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Endpiece

Students at Guy's and St Thomas's, 1819

I must be permitted to caution you against blindly adopting any system of opinion and practice which may be taught in the schools to which you may be … attached; this could be to degrade you to the ranks of empiricism. Think for yourselves.

Aesculapius. The hospital pupil's guide at St Thomas's and Guy's Hospitals. *Lond Med Repository* 1819;11:128-30

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